REMARKS

FORMAL MATTERS:

Claims 1, 3, 5-7, 9, 10, 22-23 are pending after entry of the amendments set forth herein.

Claims 8, 11-21 are canceled without prejudice.

Claims 1, 9, 10, 22 and 23 are amended. Claim 1 has been amended to incorporate the subject matter from claim 8, now cancelled. Claims 9, 10, 22 and 23 are amended to correct their dependencies or to correct typographical errors. No new matter is added.

Since claim 1 has merely been amended to recite the limitations of claim 8, the amendment to claim 1 should generate no new issues and should be entered prior to appeal.

OBJECTIONS TO THE CLAIMS

Claim 23 is objected to because of the following informalities: the term "aid" in line 1 of the claim should read "said". Claim 23 is amended accordingly and withdrawal of the objection is requested.

REJECTIONS UNDER §103(A)

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Del Vecchio et al (WO 99/01582) in view of teachings of Jin et al (Arch Biochem Biophys 20: 47-53), Kadare et al (J Virol 70: 8169-74), and Rodriguez et al. (JBC 268: 8105-10).

Claim 1 has been amended to incorporate claim 8. Since claim 8 is not included in this rejection, this rejection is moot and may be withdrawn.

Withdrawal of this rejection is requested.

Claims 6 and 7 are rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Del Vecchio in view of Jin, Kadare, and Rodriguez and further in view of Morouianu et al. (PNAS 92:4318-22).

Claim 1 has been amended to incorporate claim 8. Since claim 8 is not included in this rejection, this rejection is moot and may be withdrawn.

Withdrawal of this rejection is requested.

Claims 8-10 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Del Vecchio in view of Jin, Kadare, and Rodriguez and further in view of Wimmer et al. (US 2002/0098202). The Applicants respectfully traverse this rejection.

All prior arguments are incorporated by reference in order to preserve those arguments for appeal.

The claims are directed to a method that includes assaying a candidate agent for an effect on: a) NS4B GTPase activity *and* b) HCV replication. Thus, the claimed method clearly connects NS4B's GTPase activity and HCV replication.

The Applicants believe that the "obvious to try" standard has been improperly used here in that it has been applied to render obvious a claim that requires knowledge that the GTPase activity of NS4B - a protein that at the time of filing had no reported function and large number of potential functions - would have been predicted to have a role in viral replication. Since the Examiner has provided no evidence that NS4B's GTPase activity would have been predicted to have a role in viral replication, this rejection should be withdrawn.

The "predicted success" of a combination of elements is an important factor in determining obviousness. This principle is illustrated in *three* Supreme Court[1] cases decided prior to *KSR*, and is a recurring theme of *KSR*. For example, in *KSR* the Supreme Court stated that in order for a combination of elements to be patentable "the combination must do more than yield a predictable result". [2] Likewise, the corollary principle, namely that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results"[3] is also discussed. The Supreme Court in *KSR* also stated that that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions".[4] The "obvious to try" standard for obviousness was also addressed by the Supreme Court in *KSR*. According to the Supreme Court, "When there is a design need or market pressure to solve a problem and there are a finite number of identifiable, *predictable* solutions, a person of ordinary skill has good reason to pursue the known

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[1] *United States* v. *Adams*, 383 U.S. 39, 40 (1966); *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.C. 57, 60-62 (1969) and *Sakraida* v. *AG Pro, Inc.*, 425 U.C. 273, 282 (1976).

[2] *KSR International v. Teleflex Inc.,* 127 S. Ct. 1727, 1740 (2007).

[3] *KSR International v. Teleflex Inc.,* 127 S. Ct. 1727, 1739 (2007).

[4] *KSR International v. Teleflex Inc.,* 127 S. Ct. 1727, 1740 (2007); emphasis added.

options within his or her technical grasp". *Id* at 1742, emphasis added. As such, in order to be obvious under the "obvious to try" standard, an "invention" must be a *predictable* success.

This tenet has been followed in several post-KSR decisions recently published by the Federal Circuit. See, e.g., *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); *Eisai Co. v. Dr. Reddy's Laboratories* 2008 U.S. App. LEXIS 15399 (Fed. Cir. 2008) Pfizer v. Apotex (No. 2006-1261 Fed. Cir. 2007); *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd* (Fed. Cir. 2007).

Indeed, this standard has been adopted in the PTO's Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 (MPEP § 2141), where the MPEP advises that "Exemplary rationales that may support a conclusion of obviousness include: (E) 'Obvious to try' - choosing from a finite number of identified, *predictable solutions, with a reasonable expectation of success*" (italics added).

In greater detail, the Obviousness Guidelines states that when Office personnel reject claims using "obvious to try" rationale, the Office must resolve the Graham factual inquiries and articulate:

(1) "a finding that at the time of the invention, there had been a recognized problem or need in the art";

(2) "a finding that there had been a finite number of identified, *predictable potential* solutions to the recognized need or problem";

(3) "a finding that one of ordinary skill in the art could have pursued the known potential solutions with a *reasonable expectation of success*." (Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices at 57532, citing KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1395 (US 2007); italics added.

Thus, in order to render claims obvious using an "obvious to try" standard, there must also be a reasonable expectation of success.

As best understood by the Applicants, the Examiner believes that given the cited references, the claimed method – which requires both a GTPase assay *and* a HCV replication assay – would be *obvious to try* and therefore obvious (see Office Action, page 7, middle paragraph). This rejection should therefore be held to the standard – which requires a reasonable expectation of success - outlined above.

The Applicants believe that rejected claims are patentable because, at the time of filing, the function of NS4B, particularly the role of NS4B's GTPase activity in HCV replication, was unknown. At best, at the time of filing, there would have been a finite but large number of assays by which NS4B's function could be tested and there would have been no reasonable expectation of success for any one

assay. Alternatively, NS4B may be non-essential for any part of the viral lifecycle. Since there would be no reasonable expectation of success in testing NS4B for viral replication, the claims cannot meet the obvious to try standard outlined above.

Support for this position is found in several reviews which the Applicants believe adequately represent the state of the art at the time of filing (See reviews by Rosenberg, J. Mol. Biol. 2001 313: 451-64, Exhibit D; and by Kato Acta. Med. Okayama, 2001, 55: 133-159, Exhibit E). For example Kato in a review article in Acta. Med. Okayama, 2001, Vol. 55. No. 3, pp.133-159 states that:

> NS4B protein (261 amino acid residues for HCV-1b) is rich in hydrophobic amino acid residues and has been detected primarily in the membrane fraction [36, 39]. The function of the NS4B protein remains unknown, although it has been recently demonstrated that the NS4B protein in association with the Ha-ras gene played an important role in the malignant transformation of NIH3T3 cells [223].

and Rosenberg in J. Mol. Biol., 2001, Oct 26; 313(3):451-64 states that:

> Two of the non-structural proteins, NS4b and NS5a, are still of unknown function.

In fact, this position is supported by Del Veccio and Wimmer – two references that are cited *in support* of this rejection.

Del Vecchio on page 3, Table 1 and lines 9-10 states that

> Press, New York (1996)). However, the function of HCV NS4B protein, like that of the NS4B in the other members of the *Flaviviridae* family, is still unknown.

and Wimmer on page 1, paragraph 5 states that:

> tor of the NS3 proteinase. The functions of NS4B and p7 proteins are so far unknown. NS5B is identified as the

While the Applicants understand that there are a finite number of assays by which NS4B's function can be tested, the number of these assays is high and includes assays for transcription, translation, protein degradation, protein folding, protein transport, nucleotide metabolism, cell

metabolism, immune system evasion, to name but a few. Alternatively, NS4B may be non-essential for any part of the viral lifecycle. For that reason, one of skill in the art would not have a reasonable expectation that the GTPase activity of NS4B protein was required for HCV replication.

Since: a) the function of NS4B and the fuction of NS4B's GTPase activity were unknown at the time of filing; b) there were tens if not hundreds of assays by which the function of NS4B could be tested, and c) none of the assays would have a reasonable expectation of success in identifying the function of NS4B, the Examiner cannot reject claims 8-10 using an "obvious to try" standard.

Withdrawal of this rejection is thus requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-316.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: September 10, 2008

By: /James S. Keddie, Reg. No. 48,920/
James S. Keddie, Ph.D.
Registration No. 48,920

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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